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| 10/801,486 | 03/16/2004 | Riqiang Yan | 29915/00281B | 9882 |

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| EXAMINER | |
|---|---|
| WALICKA, MALGORZATA A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 12/22/2006 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/801,486 | YAN ET AL. | |
| | Examiner | Art Unit | |
| | Malgorzata A. Walicka | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *84-107* is/are pending in the application.

4a) Of the above claim(s) *99 and 106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-98,100-105 and 107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Amendment and response to Restriction requirement filed of Sept. 25, 2006 is acknowledged. Claims 1-83 have been cancelled and new claims 84-107 have been added. Claims 84–107 are pending. Claims 84-98, 100-105 and 107 reading on the elected species and invention are under examination.

## DETAILED ACTION

### Miscellanous

Please submit a copy of IDS of 03/16/2004, which is missing from the record.

### Priority

Applicants claim of benefits of provisional applications 60/219,795 filed 07/19/2000 and 60/275,251 filed 03/12/2001 has been noted. The priority of the instant claims to these applications has been granted.

### Election /Restriction

Applicant's election of Group III, directed to a method of assaying modulators of beta-secretase activity, in the reply filed on Sep. 25, 2006 is acknowledged. Newly submitted claim 106 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claim is directed to the method performed in a transgenic non-human mammal, and was absent from the claims as filed. The claim does not belong to the invention that has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim106 withdrawn

from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

In response to requirement of **election of species**, in result of the interview of Sep. 21, 2006 with the previous examiner and biotechnology specialist Cecilia Tsang, Applicants elected as substrates peptides having at least 6 amino acids, including four amino acids P2P1-P1'P2' which are **NL-AA**. This election was also made to comply with Petition Decision of Director Bruce Kisluk of Oct. 27, 2004 in the parental application 09/908,943. Claim 99 does not read on the elected invention an is withdrawn from examiner's consideration.

In conclusion, claims 84-98, 100-105 and 107, in part directed to the substrates comprising **NL-AA** as P2P1-P1'P2', are under examination.

The election is made with traverse. Applicants' position is,

> "Even if the computer-based sequence search based on the elected substrate peptide sequence identifies a large initial pool of literature, the pool can be expected to be easily reduced (or completely eliminated) in the context of additional limitation of the elected claims", page 14 of REMARKS.

Applicants' argument has been fully considered but is found not persuasive, because although depended claims impose limitation on the base claim 84, thus reducing the pool of literature for claims different than 84, claim 84 is not excluded from the search, and on the contrary as the claim from which other depend must be search in full. In result, the examiner is bound to consider, as Applicants put it, "a large initial pool of

literature" identified by computer–based sequence search. For all the reason the election of species is **final** at this stage of prosecution.

## Objections

1. Specification contains, on page 4, line 3 and page 86, line 24 a text from a draft version that was not deleted.

2. The specification is objected to for a vague description of the peptide substrates of the invention: "may be any length of amino acids", "may comprise a contiguous amino acid sequence of about 5-40, 45, 50, or more amino acids", both quotation from page 27, last paragraph. Furthermore, on page 28, second paragraph, "The length of the peptide maybe of any length so long as the substrate comprises a beta-secretase cleavage site that can be cleaved by a Hu-Ap2".

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

4. Please expand the abbreviation APP in claim 84 and provide the abbreviation in parenthesis.

## Rejections

### 35 USC 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Written description*

Claim 84-98, 100-105 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for assaying for modulators of beta-secretase activity, comprising:

(a) contacting a polypeptide with beta-secretase processing activity with a substrate, both in the presence and in the absence of a putative modulator compound;

wherein said substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, said amino acid sequence includes four amino acids defined by formula P2P1-P1'P2', wherein each of P2, P1, P1'and P2' are selected from large group of amino acids wherein preferably P2 is N, P1 is L, P1' is A and P2' is A (**NL-AA**), wherein the substrate is cleaved between P1 and P1' by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) and wherein said peptide does not comprise the corresponding P2P1-P1'P2' portion of the amino acid sequences SEQ ID NOs: 19-39.

The claims are directed to the use of:

a) an extremely large genus substrates comprising elected tetrapeptide P2P1-P1'P2' of NL-AA and any at least sextapeptide P3P2P1-P1'P2'P3' wherein peptides are combinations of any amino acids as recited by the claims and are cleaved between P1 and P1' by Hu-Asp2 , i.e. the substrates are of any length greater than 6 amino acid excluding the amino acid sequences SEQ ID NOs: 19-39,

b) a genus of polypeptides having beta secretase processing activity.

Regarding genus a) the specification does not teach that the tetrapeptide NL-AA is cleaved by a human aspartyl protease encoded by SEQ ID NO: 1 or 3 of the specification. For that reasons Applicants do not teach a substrate comprising NL-AA and being of any length, i.e., of length lacking of written description in the disclosure; see the above objection to the specification.

Even if the tetrapeptide NL-AA were shown to be cleaved by HU-Ap2, the presence of other amino acids, i.e., flanking sequences on both sides, wherein said sequences have unknown structure, might affect negatively activity of Hu-Asp2, or any polypeptide with beta-secretase APP processing activity, on the substrate comprising said tetrapeptide. This fact is known to those skilled in the art and emphasized by Applicants themselves, "The observation reaffirms that amino acid optimization at certain position depends on the rest of the substrate sequence" page 86, line 21 of the specification. Altogether, the functional limitation "is cleaved by HuAs2" plus the structural limitation for the core of substrate: NL-AA, are not sufficient to identify the whole broadly claimed genus of Hu-Asp2 substrates that comprise NL-AA and are to be used in the claimed invention. Some of the unelected peptide substrates are shown to

by de Applicants to be cleaved by Hu-Asp2, however the presence of other amino acids, i.e., flanking sequences on both sides, wherein said sequences have unknown structure, might affect negatively activity of Hu-Asp2, or any polypeptide with beta-secretase APP processing activity, on larger sequences comprising said cleavable peptides for the reasons that have just been explained.

Regarding genus b), Applicants claim the use of **any** polypeptide with beta-secretase APP processing activity, however it is not certain that any beta secretase that cleaves APP between amino acid residues 596 and 597 will do the same with a peptide of any length containing NL-AA or other P2P1-P1'P2', P3P2P1-P1'P2'P3' or P4 P3P2P1-P1'P2'P3'P4' as broadly claimed. There is not showing that Hu-Asp2(a) identified by SEQ ID No: 2 or Hu Asp2(b) identified by SEQ ID NO:4 do cleave NL-AA, neither Applicants teach that SEQ ID NO: 4 has the same genus of substrates as SEQ ID NO:2. SEQ ID NO: 4 is a splice variant that lacks amino acids 190-214 of SEQ ID NO: 2, which seems to position the signature catalytic triplexes differently than in SEQ ID NO: 2, which may affect activity.

Furthermore, Applicants do not teach in their disclosure any polypeptide having beta-secreatase APP processing activity. Applicants teach two splice variants of human beta secretase: of SEQ ID NO: 2 and 4 (501 amino acids and 476 amino acids). These amino acid sequences are obtained by translation of the encoded cDNAs of SEQ ID NO: 1 and 3. Furthermore, Applicants teach mouse beta secretase of SEQ ID NO: 199 of 501 amino acids. Applicants do not teach any other beta secretase. The teaching of three species that cleave APP at positions 596-597 (KM-DA) for normal APP and (NL-

DA) for its Swedish mutation does not identify the whole genus of enzymes that may also cleave any peptide comprising NL-AA or other broadly claimed substrates.

Claim 100 is specifically rejected because Applicants do not show that any beta secreatase cleaves any NL-AA comprising peptide at the rate that is higher than the rate of cleavage of SEVKM-DAEFR.

In summary, Applicants are kindly reminded that written description requirement is not satisfied by merely providing "a result that one might achieve if one made that invention"; see Eli Lilly, 119 F.3d at 1568. 43 USPQ2d at 1406 as quoted in MPEP page 2100-173 paragraph (2), and that is exactly what Applicants expect from one skilled in the art. In conclusion, one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

*Lack of enablement*

Claims 84-98, 100-105 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Therefore, to make and use the claimed inventions requires undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses use of

a) an extremely large genus substrates comprising elected tetrapeptide P2P1-P1'P2' of NL-AA and any at least sextapeptide P3P2P1-P1'P2'P3' wherein peptides are combinations of any amino acids as recited by the claims and are cleaved between P1 and P1' by Hu-Asp2, i.e. the substrates are of any length greater than 6 amino acid excluding the amino acid sequences SEQ ID NOs: 19-39, and

b) a genus of polypeptides having beta secretase processing activity

in an assay for identifying a compound that modulates activity of beta secreatse.

Although the art of constructing peptides is well developed, to make and use the claimed invention one skilled in the art is forced to do research outside the realm of routine experimentation absent teaching of the structure of the peptides to be used as substrates. Although the disclosure teaches explicitly many peptides that may be used in the claimed invention, the disclosure does not teach that a peptide of any length comprising tetrapeptide NL-AA is a substrate for Hu-ASP2 as required by the claims. The broad scope of the claims covers an extremely large genus of peptides comprising NL-AA, for which the disclosure does not provide guidance as to the structure o peptide

regions flanking the N- and C-termini of NL-AA. The art teaches unpredictability in constructing enzymatic substrates with any amino acid substitutions, additions and insertions in P1P2-P1'P2' site and in its flanking regions. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the construction of peptides being beta secretase substrates and containing as the cleavage site NL-AA should proceed so that the claimed species have the structure that is proper for use in the broadly claimed invention. As pinpoint in the above rejection for lack of written description, what Applicants expect from one skilled in the art is "a result that one might achieve if one made that invention"; see Eli Lilly, 119 F.3d at 1568. 43 USPQ2d at 1406 as quoted in MPEP page 2100-173 paragraph (2).

Furthermore, Applicants do not provide in their disclosure sufficient guidance for the structure of any polypeptide having beta-secreatase APP processing activity, i.e. for all beta secretases form natural sources and manmade. Applicants teach two splice variants of human beta secretase: of SEQ ID NO: 2 and 4 (501 amino acids and 476 amino acids). Applicants teach also mouse beta secretase of SEQ ID NO: 199 of 501 amino acids. Applicants do not teach any other beta secretase. Examples of three beta secretases fail providing sufficient instruction as to the structure of any beta secretase as broadly recited by the claims. Since all the beta-secreatases that are to be used in the claimed invention are to be able to cleave the extremely large genus of substrates, one having skills in the art is forced to examine activity of any potential beta secretase

on any substrate. Such experimentation has low probability of success without a further guidance on the structure of beta secretase that is to be applied.

In summary, without further a guidance on the part of Applicants in regards of structure of the substrate polypeptides and beta secretase polypeptides, experimentation left to those in the art is improperly extensive and undue.

***35 USC 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 85-93, 95, 96-98, 102-105 and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by the US Patent 7,067,271 ('271) issued to Anderson et al, with the valid priority to the US provisional application 60/139,172 filed on Jun. 15,1999.

The claims are directed to a method for assaying for modulators of beta-secretase activity, comprising:

(a) contacting a polypeptide with beta-secretase processing activity with a substrate, both in the presence and in the absence of a putative modulator compound;

wherein said substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, said amino acid sequence including four amino acids defined by formula P2P1-P1'P2', wherein P2 is N, P1 is L, P1' is A and P2' is A (**NL-AA**), wherein the substrate is cleaved between P1 and P1' by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) and wherein

said peptide does not comprise the corresponding P2P1-P1'P2' portion of the amino acid sequences SEQ ID NOs: 19-39. The patent teaches a method for assaying for inhibitors of a betasecretase polypeptide, wherein the substrate has SEQ ID No: 88 (SEV**NLAA**EF) which is cleaved by beta secretasae of the amino acid sequence identical to SEQ ID NO: 2. (HuAsp2); see claim 3

The '271 does disclose not only substrate SEV**NLAA**EF which reads on all limitations imposed on the substrate by claims 84-93, but the patent also discloses natural and artificial truncated forms of human beta secretase of SEQ ID NO: 2 ( SEQ ID NOs: 43, 57-60 and 66-75) of the instant invention and their encoding DNA molecules.

In addition, the patent teaches cells which express both beta secretase and APP to be used in the assays for beta secretase inhibitors; see the paragraph bridging column 36 and 37.

Furthermore the patent teaches the substates of beta secretase that have optional detectable fluorescent tags or chromogenic tags; see column 51, section C. Assays Using Synthetic Oligopepitde Substrates.

The patents teaches all details of the rejected claims.

**Statutory Double Patenting**

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

*Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 84-105 and 107 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 84-105 and 107 of copending Applications No. 10/801,509 and 10/801,938. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

**Conclusion**

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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